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Patent Application
Attorney Docket No. 10925A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: M. Perros et al. :

APPLICATION NO.: NOT YET ASSIGNED : Examiner: NOT YET ASSIGNED

FILING DATE: Herewith : Group Art Unit: Not Yet Assigned

TITLE: TROPANE DERIVATIVES USEFUL IN THERAPY :

Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please ENTER the following amendments to the subject application as follows:

In the specification:

- At page 1, line 1, please insert the following text:

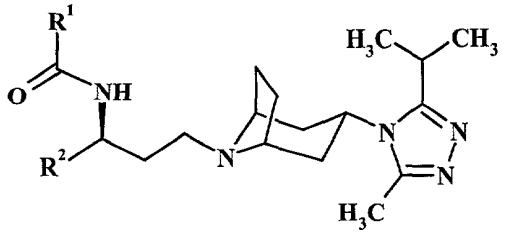
Cross Reference To Related Applications

This application claims the benefit of priority of foreign application numbers GB 0014046.7 and GB 0015835.2, filed in Great Britain on May 26, 2000 and June 27, 2000, respectively. This application also claims the benefit of priority of U.S. Provisional Application Nos. 60/214,587 and 60/219,202, filed June 27, 2000 and July 19, 2000, respectively.

In the claims:

- Please cancel claims 10-18 and 23-37 without prejudice.
- Please amend claims 1-9 and 19-22, and add new claims 38-56 as follows:

1. (Amended) A compound of the formula:



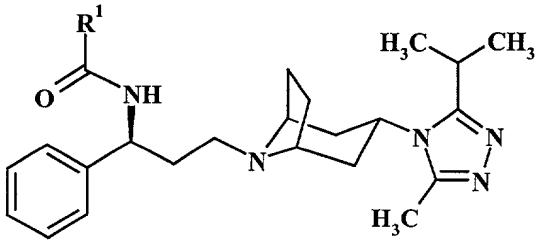
I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is C_{3-6} cycloalkyl optionally substituted by one or more fluorine atoms, or C_{1-6} alkyl optionally substituted by one or more fluorine atoms, or C_{3-6} cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and

R^2 is phenyl optionally substituted by one or more fluorine atoms.

2. (Amended) The compound of claim 1 of the formula:



IA

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is either C_{3-6} cycloalkyl optionally substituted by one or more fluorine atoms, or C_{1-6} alkyl optionally substituted by one or more fluorine atoms.

3. (Amended) The compound of claim 1, wherein R^1 is either C_{4-6} cycloalkyl optionally substituted by one or two fluorine atoms, or C_{1-4} alkyl optionally substituted by from one to three fluorine atoms.

4. (Amended) The compound of claim 3, wherein R^1 is either cyclobutyl, cyclopentyl, 4,4-difluorocyclohexyl or 3,3,3-trifluoropropyl.

5. (Amended) The compound of claim 1, wherein R^2 is phenyl optionally substituted by 1 or 2 fluorine atoms.

6. (Amended) The compound of claim 5, wherein R^2 is phenyl or monofluorophenyl.

7. (Amended) The compound of claim 6, wherein R^2 is phenyl or 3-fluorophenyl.

8. (Amended) The compound of claim 1 which is selected from the group consisting of:

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide;

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide;

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4,4-trifluorobutanamide;
N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide;
and
N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}-4,4-difluorocyclohexanecarboxamide;
or a pharmaceutically acceptable salt or solvate of any thereof.

9. (Amended) A pharmaceutical composition comprising a compound of claim 1 and one of a pharmaceutically acceptable excipient, a pharmaceutically acceptable diluent or a pharmaceutically acceptable carrier.

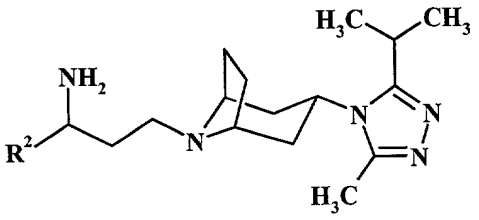
19. (Amended) A method of treating in a mammal a disorder in which the modulation of CCR5 receptors is implicated, which comprises administering to said mammal an effective amount of a compound claim 1.

20. (Amended) A method of treating HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease, in a mammal, which comprises administering to said mammal an effective amount of a compound of claim 1.

21. (Amended) A method of treating, in a mammal, a respiratory disorder selected from adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis, which comprises administering to said mammal an effective amount of a compound of claim 1.

22. (Amended) A method of treating, in a mammal, an inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, graft rejection, including a kidney or a lung allograft, endometriosis, type I diabetes, a renal disease, chronic pancreatitis, an inflammatory lung condition or chronic heart failure which comprises administering to said mammal an effective amount of a compound of claim 1.

38. A compound of the formula:

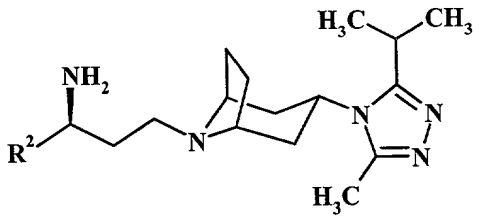


(IIA).

wherein R^2 is phenyl optionally substituted by one or more fluorine atoms.

39. The compound of claim 38, wherein R^2 is phenyl.

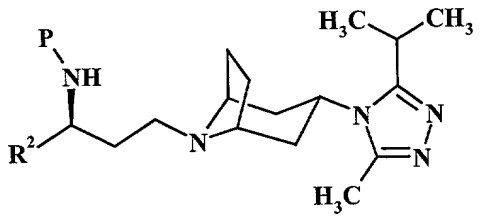
40. The compound of claim 38 of the formula:



(II).

41. The compound of claim 40, wherein R^2 is phenyl.

42. A compound of the formula:



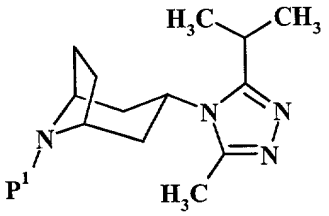
(VII)

wherein R^2 is phenyl optionally substituted by one or more fluorine atoms; and P is a protecting group.

43. The compound of claim 42, wherein R^2 is phenyl.

44. The compound of claim 42, wherein P is t-butyloxycarbonyl or benzyloxycarbonyl.

45. A compound of the formula:

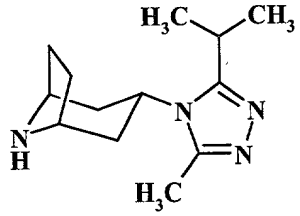


(XII)

wherein P^1 is hydrogen or a protecting group.

46. The compound of claim 45, wherein P^1 is benzyl.

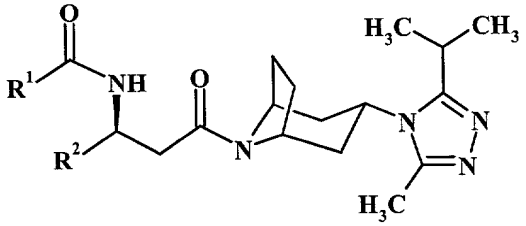
47. The compound of claim 45, or a salt thereof, having the formula:



(VIA)

48. The p-toluenesulphonate salt of the compound of claim 47.

49. A compound of the formula:



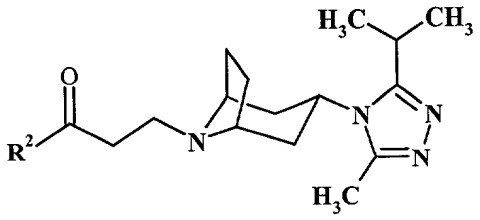
(XIV)

wherein R^1 is C_{3-6} cycloalkyl optionally substituted by one or more fluorine atoms, or C_{1-6} alkyl optionally substituted by one or more fluorine atoms, or C_{3-6} cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and

R^2 is phenyl optionally substituted by one or more fluorine atoms.

50. The compound of claim 49, wherein R^2 is phenyl.

51. A compound of the formula:

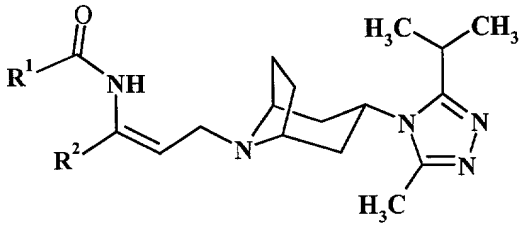


(XVIII)

where R^2 is phenyl optionally substituted by one or more fluorine atoms.

52. The compound of claim 51, wherein R^2 is phenyl.

53. A compound of the formula:

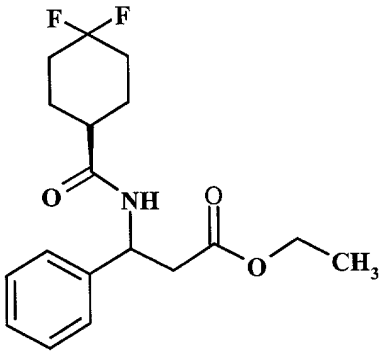


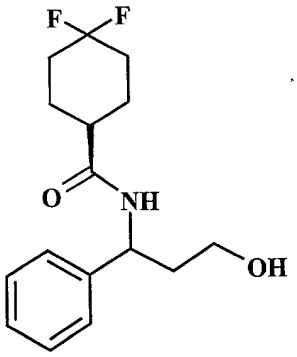
(XIX)

wherein R^1 is C_{3-6} cycloalkyl optionally substituted by one or more fluorine atoms, or C_{1-6} alkyl optionally substituted by one or more fluorine atoms, or C_{3-6} cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms; and R^2 is phenyl optionally substituted by one or more fluorine atoms.

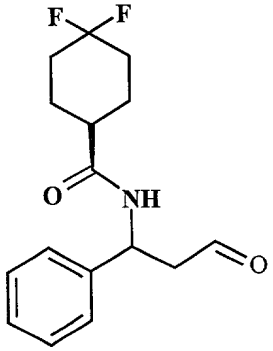
54. The compound of claim 53, wherein R^2 is phenyl.

55. A compound selected from the group consisting of:



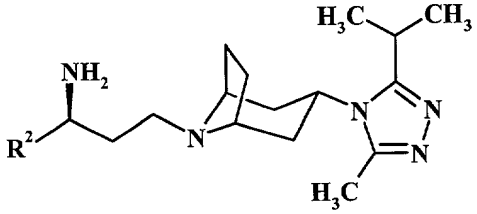


; and



56. A process for the preparation of a compound of claim 1 selected from a process which comprises:

(a) coupling a compound of the formula:



II

with a compound of formula:

R^1CO_2H (III);

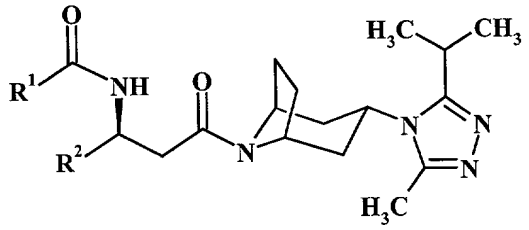
or

(b) reaction of a compound of the formula (II) with a compound of the formula:

R^1COZ (VIB)

where Z is a carboxylic acid activating, group; or

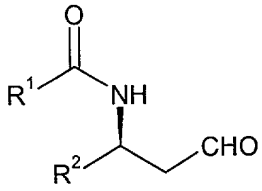
(c) reduction of a compound of the formula:



(XIV)

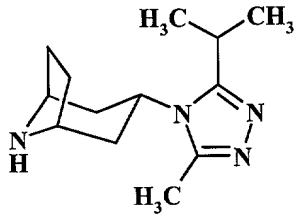
;

(d) reductive amination using a compound of the formula:



(XVI)

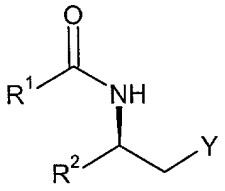
and a compound of the formula:



(VIA)

or a salt thereof; or

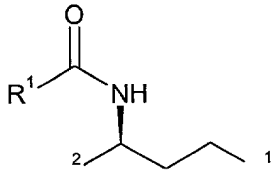
(e) reductive amination using a compound of the formula:



(XV)

where Y is CN, and a compound of the formula (VIA), or a salt thereof; or

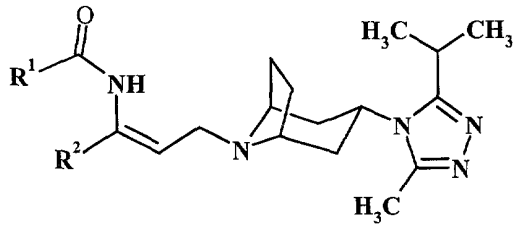
(f) alkylation of a compound of the formula (VIA), or a salt thereof, with a compound of the formula:



(XVII)

where Z^1 is a leaving group; or

(g) asymmetric reduction of a compound of the formula:



(XIX)

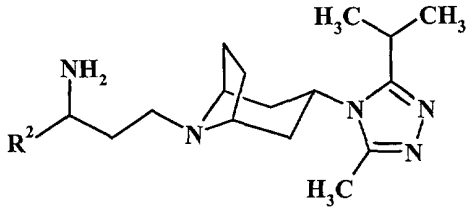
; or

(h) reaction of a compound of the formula (II), or a metal salt thereof, with a compound of the formula:

$R^1CO_2R^5$
(XXIV)

where R^5 is an ester forming group; or

(i) reaction of a compound of the formula:



(IIA)

either with a compound of the formula (III) under coupling conditions, or a compound of the formula (VIB), and in the presence of a a chiral catalyst:

wherein any one of processes (a) through (i) is optionally followed by conversion of a compound of claim 1 a pharmaceutically acceptable salt thereof.

REMARKS

Claims 1 – 37 were submitted with the original specification of this application. Applicants have hereinabove canceled claims 10-18 and 23-37 without prejudice to applicants' right to pursue the subject matter of the canceled claims in one or more divisional or continuation applications, and have amended claims 1-9 and 19-22 and added new claims 38-56. Accordingly, upon entry of this amendment, claims 1-9, 19-22 and 38-56 are pending.

Applicants maintain that the amendment of claims 1-9 and 19-22, and the addition of new claims 38-56 raises no issue of new matter. All of the amendments and additions are made to conform the claims to U.S. practice and to reduce the number of independent claims so as to reduce excess claims fees. Claims 23 to 37 have been replaced with new claims 38-56, with the correspondence indicated below:

- New claim 38 corresponds to original claim 24;
- New claims 39, 41, 43, 50, 52 and 54 correspond to original claim 31;
- New claim 40 corresponds to original claim 23;
- New claim 42 corresponds to original claim 25;
- New claim 44 corresponds to original claim 33;
- New claim 45 corresponds to original claim 27;
- New claim 46 corresponds to original claim 32;
- New claim 47 corresponds to original claim 26;
- New claim 48 is new, and was added to properly claim a preferred embodiment of the invention of original claim 26;
- New claim 49 corresponds to original claim 28;
- New claim 51 corresponds to original claim 29;
- New claim 53 corresponds to original claim 30;
- New claim 55 corresponds to original claims 34, 35 and 36; and
- New claim 56 corresponds to original claim 37.

Applicants submit that the differences between the new claims and the original claims merely reflect rewording of the claims to U.S. practice, to eliminate multiple dependencies, and to reduce the filing fee by rewriting some independent claims in dependent form. Support for new claim 24 may be found in original claim 26. Accordingly, applicants respectfully request entry of the replacement claims.

Attached hereto is a marked-up version of original claims 1-9 and 9-22 showing the changes made, captioned "**PLEASE DO NOT ENTER - Version with markings to show changes made**."

The filing fee has been calculated on the basis of the replacement claims. No additional fee is believed necessary in connection with this amendment. However, the fee transmittal submitted herewith authorizes payment of any additional fees.

Applicants earnestly solicit favorable action on the merits.

Respectfully submitted,

Date: May 25, 2001

Jeffrey N. Myers
Attorney for Applicant(s)
Reg. No. 41,213

Pfizer, Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755
(212) 733-5061

PLEASE DO NOT ENTER - Version with markings to show changes made

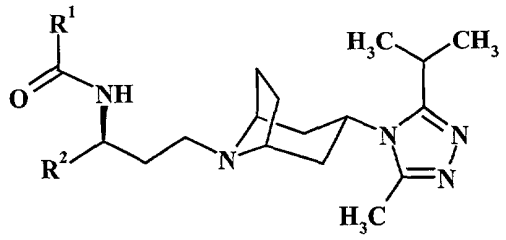
Marked-up version of amended claims – PLEASE DO NOT ENTER

Guide to claim amendments:

Insertions – underlined

Deletions – ~~strikethrough~~

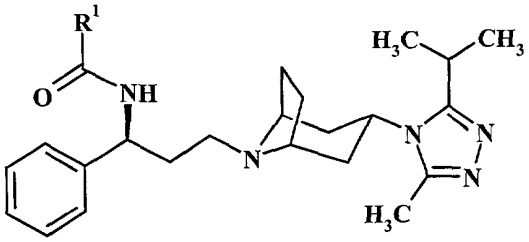
1. (Amended) A compound of the formula:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:
R^1 is C_{3-6} cycloalkyl optionally substituted by one or more fluorine atoms, or C_{1-6} alkyl optionally substituted by one or more fluorine atoms, or C_{3-6} cycloalkylmethyl optionally ring-substituted by one or more fluorine atoms;
and
R^2 is phenyl optionally substituted by one or more fluorine atoms~~:~~
~~or a pharmaceutically acceptable salt or solvate thereof~~.

2. (Amended) A~~The~~ compound ~~as claimed in~~of claim 1 of the formula:



IA

or a pharmaceutically acceptable salt or solvate thereof, wherein:
~~-~~R^1 ~~represents~~is either C_{3-6} cycloalkyl optionally substituted by one or more fluorine atoms, or C_{1-6} alkyl optionally substituted by one or more fluorine atoms~~, or a pharmaceutically acceptable salt or solvate thereof~~.

3. (Amended) A~~The~~ compound ~~as claimed in~~of claim 1, wherein R^1 is either C_{4-6} cycloalkyl optionally substituted by one or two fluorine atoms, or C_{1-4} alkyl optionally substituted by from one to three fluorine atoms.

4. (Amended) AThe compound ~~as claimed in~~of claim 3, wherein R^1 is either cyclobutyl, cyclopentyl, 4,4-difluorocyclohexyl or 3,3,3-trifluoropropyl.

5. (Amended) AThe compound ~~as claimed in~~of claim 1, ~~3 or 4~~ wherein R^2 is phenyl optionally substituted by 1 or 2 fluorine atom~~(s)~~.

6. (Amended) AThe compound ~~as claimed in~~of claim 5, wherein R^2 is phenyl or monofluorophenyl.

7. (Amended) AThe compound ~~as claimed in~~of claim 6, wherein R^2 is phenyl or 3-fluorophenyl.

8. (Amended) AThe compound ~~as claimed in~~of claim 1 which is selected from the group consisting of:

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide;

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide;

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4,4-trifluorobutanamide;

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide;

and

N-{(1S)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}-4,4-difluorocyclohexanecarboxamide~~:~~;

or a pharmaceutically acceptable salt or solvate of any thereof.

9. (Amended) A pharmaceutical composition ~~including~~comprising a compound of ~~the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in any preceding~~ claim 1, ~~together with~~ and one of a pharmaceutically acceptable excipient, a pharmaceutically acceptable diluent or a pharmaceutically acceptable carrier.

19. (Amended) A method of treating~~ment of~~ in a mammal ~~to treat~~ a disorder in which the modulation of CCR5 receptors is implicated, ~~including treating~~which comprises administering to said mammal ~~with~~ an effective amount of a compound ~~of the formula (I)~~

~~or with a pharmaceutically acceptable salt, solvate or composition thereof as claimed in any one of~~ claims ~~1 to 8 and 9, respectively~~.

20. (Amended) A method of treating~~ment of a mammal to treat~~ HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease, in a mammal, which comprises administering to ~~including treating~~ said mammal ~~with~~ an effective amount of a compound of ~~the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof as claimed in any one of~~ claims ~~1 to 8 and 9, respectively~~.

21. (Amended) A method of treating, in a mammal,~~ment of a mammal to treat~~ a respiratory disorder ~~including~~selected from adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis ~~or~~and chronic sinusitis, ~~including treating~~ which comprises administering to said mammal ~~with~~ an effective amount of a compound of ~~the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof as claimed in any one of~~ claims ~~1 to 8 and 9, respectively~~.

22. (Amended) A method of treating, in a mammal, ~~ment of a mammal to treat~~ an inflammatory bowel disease~~, including Crohn's disease or ulcerative colitis~~, multiple sclerosis, rheumatoid arthritis, graft rejection, including a kidney or a lung allograft, endometriosis, type I diabetes, a renal disease, chronic pancreatitis, an inflammatory lung condition or chronic heart failure ~~including treating~~which comprises administering to said mammal ~~with~~ an effective amount of a compound of ~~the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof as claimed in any one of~~ claims ~~1 to 8 and 9, respectively~~.